PELLAGRA THERAPY.

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This report is based on a study of 251 patients suffering from pellagra. All the patients were hospitalized and studied under conditions where the effect of different types of treatment could be evaluated.

The routine hospital diet with its abundance of red meat, milk, fresh fruit and vegetables is inherently a pellagra curative diet and cannot be used if one wishes to measure the curative effect of any specific type of treatment. Early in 1931, we devised a diet similar to that which the patients were consuming at the time the symptoms of pellagra appeared. This diet, which will be referred to as the Standard Basic Diet No. 1 (Table 1), was even more deficient in the vitamin B complex than the diet with which Goldberger produced pellagra.[12] By supplementing the diet with the other known vitamins and minerals we hoped to obtain a deficiency which was limited to the pellagra preventive factor of Goldberger.

Patients having the characteristic dermatitis of pellagra over the exposed surfaces of the body, and one or more constitutional symptoms of the disease, such as glossitis, anorexia, diarrhea, nausea, vomiting, abdominal pain, or mental disturbances were hospitalized and fed the deficient diet. Usually the patients were kept on the deficient diet, without treatment, from 3 to 10 days to evaluate the status of the disease. Treatment was started as soon as it became evident that the disease was progressing. In nearly all instances the skin lesions improved. This was true regardless of whether the general symptoms were growing progressively worse or retrogressing. A similar observation was made by Spies[31,32] who employed an even more restricted diet.

The patients who were apparently improving on the basic diet, without specific treatment, were tested with graded exposures to sunlight. One arm or leg was exposed to the direct rays of the sun on three or four consecutive days. The initial exposure varied from 15 to

TABLE. 1.

STANDARD BASIC DIET NO. 1.

Article	Quantity (g.)	Protein (g.)	Fat (g.)	Carbohydrate (g.)	Minerals (grams) Ca	P	Fe	Vitamins A	B	C	D	P.P.	Calories
Corn meal	92	8.3	2.0	69.0	0.011	0.1225	0.0006	.....	+	.....	.....	±	
Cane syrup	105	...	...	89.2	.....	.....	.....	.....	+	.....	.....	+	
Flour	111	12.5	1.2	83.4	0.022	0.1030	0.0010	.....	+	.....	.....	—	
Lard	81	...	81.0	...	.....	.....	.....	.....	—	.....	.....	—	
Rice	25	2.0	0.1	19.6	0.0023	0.0240	0.0002	.....	—	.....	.....	—	
Field peas	90	19.2	1.4	54.6	0.0756	0.0760	0.0052	+	++	.....	.....	+	
Hominy grits	51	4.3	0.3	40.6	0.0056	0.0734	0.0005	+	—	.....	.....	—	
Fat salt pork	60	1.1	51.3	0.0	0.0011	0.0115	0.0001	.....	—	.....	.....	—	
													2890.0
Cod liver oil	90 cc.	...	90.0	...	.....	0.0117	.....	++++	..	.....	++++	—	810.0
Tomato juice	45 cc.	0.4	0.1	2.0	0.005	.....	0.0002	++	++	++++	.....	+	10.3
Iron ammonium citrate	6	...	...	...	.....	.....	1.02	.....	.....	.....	.....	—	
Calcium gluconate	6	...	...	...	0.5580	.....	.....	.....	.....	.....	.....	—	
Cheese	60	17.4	21.6	...	0.5586	0.4098	0.0007	++	++	.....	.....	+	264.0
Total		65.2	249.0	358.40	1.2392	0.8319	1.0285	++++	+++	++++	++++	+	3974.3

30 minutes and the maximum time of exposure never exceeded two hours.[37] A definite dermatitis developed over the exposed areas in 34 of the 81 pellagrins tested (42 per cent). In 10 patients the dermatitis was produced on apparently normal skin which had previously been protected by clothing. Two patients showed an accentuation of the constitutional symptoms without the development of a dermatitis following exposure. Among the 36 patients who were reactivated by exposure to sunlight there was an increase in anorexia in 21, diarrhea in 21, glossitis in 27, nausea and vomiting in 10, and dementia developed in 4. Neither cutaneous lesions nor general symptoms occurred in any of these 36 patients after re-exposure to maximum doses of sunlight following adequate treatment.

In the group of 81 pellagrins exposed to direct sunlight, 45 failed to develop either local dermatitis or constitutional symptoms. All the patients in this group recovered completely while subsisting upon the deficient diet. Similar, spontaneous recoveries have been reported by Matthews[18] and by Sydenstricker and his associates.[40] It is obvious that any attempt to test the efficiency of a curative substance in this type of patient would have been futile.

Our efforts to evaluate the curative materials have been restricted to those patients (1) who were growing rapidly worse while subsisting on the basic deficient diet and (2) those who were reactivated by exposure to direct sunlight while under observation in the hospital and maintained on the deficient diet. The criteria of cure were a prompt disappearance of all signs and symptoms of the disease and the demonstration by controlled exposure that the patient was no longer susceptible to the deleterious effects of sunlight.

Yeast Therapy.

Goldberger's introduction of yeast as a method of preventing and curing pellagra served to emphasize the dietary etiology of the disease. Yeast, however, is not a very effective treatment for the critically ill pellagrin. In a series of patients studied by Blackford[2] at the University of Virginia, there was very little, if any, difference in mortality or duration of the disease between the group which received the usual hospital diet and those which received in addition a daily supplement of yeast.

Liver Extracts.

The use of liver extracts in the treatment of pellagra was introduced by Voegtlin[41] in 1914. While good results were reported, this form of therapy was not employed widely until many years later, probably due to the fact that liver extracts were not readily available until they were prepared commercially for the treatment of pernicious anemia. In 1930, Goldberger and Sebrell[11] showed that experimental blacktongue in dogs could be prevented and cured by a powdered extract of liver (Lilly's 343). Two years later Boggs and Padget[3] reported that this powdered extract was very effective as a supplement to a well-rounded hospital diet. This powdered extract will cure pellagra when the patient is under controlled conditions and subsisting on a deficient diet as shown by the studies of Ruffin and Smith in 1934[21] and Fouts and his associates in 1936.[8]

Ruffin and Smith reported the use of an aqueous extract of whole liver (solution of liver extract — Valentine N. N. R.) in 1932,[26] 1934[21] and 1937.[22] Thirty cc. of this extract was administered three times each day for a period of 7 to 10 days. Rapid and complete recovery was noted in 20 of 22 patients, and none relapsed after exposure to sunshine following treatment. The response to this therapy was prompt and in many instances dramatic. The glossitis subsided within 2 to 4 days; the appetite returned after 3 to 5 days; the diarrhea usually ceased within 7 to 10 days; and the dementia frequently disappeared after 2 to 3 weeks of therapy. When the dementia had existed for a month or longer, rarely was any improvement noted, although the other symptoms of pellagra disappeared promptly.

The beneficial effects of parenteral extracts in the treatment of pellagra, when the patient is subsisting on a general diet, were first reported by Ramsdell and Magness[30] in 1933. This was soon confirmed by other observers.[33,9,13,29,42] Spies[37,38] and his associates used large doses intravenously with dramatic results and have reported a reduction in mortality from 32 per cent to 6 per cent with this method of therapy.[38] However, it is important to note that these patients were fed a well-balanced diet, and therefore their recovery cannot be attributed entirely to the liver extract. When the various parenteral extracts, known to be effective in the treatment of pernicious anemia, were tested by our method on known active cases subsisting on the

deficient diet they were found to be only partially effective in inducing a remission. In a series of 23 pellagrins, the acute glossitis subsided promptly in 18. It was noted that the failure of the tongue to improve occurred in those patients receiving the extract from less than 400 grams of liver. There was little if any improvement in the appetite, even after enormous doses (derived from 4200 grams) of liver extract, a result which is in sharp contrast to the effects of liver extracts in the treatment of pernicious anemia and sprue. No constant effect on the diarrhea was observed, but it was our impression that the larger doses, given parenterally, usually resulted in improvement. The patients who showed marked improvement in the glossitis and some improvement in the general symptoms promptly relapsed after exposure to direct sunlight with dermatitis, glossitis, increased diarrhea and frequently nausea and vomiting. After treatment with the aqueous extract of whole liver these symptoms promptly subsided and did not recur with re-exposure to sunlight.

Additional studies showed that the residue left over after the preparation of the parenteral fraction of liver was not effective in curing pellagra in doses comparable to those of the whole aqueous extract which were effective.[22] This suggested the possibility that there were two or more factors in liver which were necessary for the cure of pellagra. We were investigating this possibility with the coöperation of Dr. Y. SubbaRow of Harvard when Elvehjem and his associates[7] discovered that nicotinic acid would cure experimental blacktongue.

Nicotinic Acid Therapy.

In September 1937 Elvehjem and his associates reported the cure of experimental blacktongue with nicotinic acid. Their results were soon confirmed by other investigators.[4,6,30] Smith, Margolis and Margolis[30] found the drug to be effective and harmless when administered orally, intramuscularly or intravenously and Dann and SubbaRow demonstrated that nicotinic acid was ineffective in the treatment of so-called "rat dermatitis" and "chick dermatitis," which at one time were considered analogous to human pellagra.[4]

The original work of Elvehjem gave no indication of the minimal dose or the range of effective doses. Margolis, Margolis and Smith[16] treated 26 dogs in 35 acute attacks of experimental blacktongue and compared the results with those obtained in 18 dogs treated with the

most effective liver fractions. The daily dose employed in the dog varied from 0.1 mgm. to 10 mgm. per kilogram of body weight. The 0.1 mgm. dose failed to cure and the 0.2 mgm. dose was slowly effective. Doses of 0.5 mgm. resulted in rapid and dramatic cures, and doses twenty times as large (10 mgm.) were no more effective.

In an effort to determine the effect of large doses of nicotinic acid in normal individuals, 13 medical students, who volunteered, were selected for experimental study. Ten were given one gram of nicotinic acid per day in capsules, divided into four doses, and three were given lactose in similar capsules, so that the student was unaware of what he was receiving. The three controls experienced no reactions whatever. Each of the students taking nicotinic acid complained of flushing of the face and neck. However, much more serious symptoms were noted: marked mental depression, epigastric distress, substernal oppression, headache, nausea and vomiting. Although the experiment was planned for 10 days, five of the students felt so badly that they stopped taking the capsules after the second day.

In contrast to these observations, Bean[1] reports that little or no ill effects were noted after the use of large doses in normal individuals. However, Sydenstricker and his associates[10] found that 0.25 to 1 gram doses in normal controls produced definite toxic symptoms similar to those reported by us. The observations made at Duke Hospital, and those of Sydenstricker, would indicate that nicotinic acid is definitely toxic and the indiscriminate use of large doses is to be avoided.

The beneficial effects of nicotinic acid in the treatment of human pellagra were demonstrated independently and simultaneously by four different groups of workers. The first published report showing the potency of this material was by Fouts and his associates[7] in November 1937. On December 18, 1937, there appeared two communications, one by Harris[11] and the other by Smith, Ruffin and Smith,[28] reporting the effectiveness of nicotinic acid in pellagra. Spies, Cooper and Blankenhorn[30] reported a series of 17 cases in February 1938. Since then there have been numerous reports of the successful use of nicotinic acid in the treatment of pellagra.[10,15,18,19,23,24,36,37,40]

It is interesting to note that doses of 500 to 1000 mgm. per day were employed by Fouts and his associates, by Harris, and by Spies, Cooper and Blankenhorn. In contrast to these large doses, the patient

reported by Smith, Ruffin and Smith recovered promptly after the administration of only 70 mgm. per day, or 1.5 mgm. per kilogram. Even this apparently small dose is three times the dog curative dose (0.5 mgm.) reported by Margolis, Margolis and Smith.[16] The efficacy of the small dose treatment has been confirmed by subsequent studies at Duke Hospital and by Frances, Bates, Barker, and Matthews[17] of the Johns Hopkins Hospital.

From November 1, 1937, to September 1, 1939, 141 patients with pellagra have been studied at the Duke Hospital. All the patients in this group had the characteristic dermatitis and one or more constitutional symptoms. However, 73 of these were either mild or subsiding cases and were not included in this study. The remaining 68 patients were hospitalized. Twenty-two of the hospitalized patients had complicating diseases rendering them unsuitable for experimental study, and therefore were fed an amplified diet. Eight of this group were given nicotinic acid, 30 to 80 mgm. daily, and all recovered. Three were given both nicotinic acid and liver extracts and promptly recovered. Eleven were treated with various extracts of liver. One patient in this group was moribund on admission and another died of generalized peritonitis. The other nine recovered.

The remaining 46 patients were fed a basic diet deficient in the B complex (Table 2). In this group 23 patients improved on the basic diet and failed to relapse after exposure to sunlight. They were then fed an amplified diet supplemented by nicotinic acid, and all made a satisfactory recovery. The remaining 23 patients were considered as active pellagrins and suitable for study. It should be emphasized that of *141 patients suffering from clinical pellagra, only 23 were found suitable for the critical evaluation of the therapeutic efficacy of nicotinic acid.*

Results of Treatment with Nicotinic Acid.

The response to treatment with nicotinic acid is prompt and in many instances dramatic. Within 24 hours after the first dose the fiery redness of the tongue disappears and ulcers beneath the tongue and on the lips usually heal after 3 to 5 days. The papillae will regenerate within 7 to 14 days.

The anorexia which is a very constant symptom in active pellagra disappears within 3 to 5 days except in an occasional patient in

TABLE 2.

STANDARD BASIC DIET NO. 3.

Article	Quantity (g.)	Protein (g.)	Fat (g.)	Carbohydrate (g.)	Minerals (grams) Ca	P	Fe	Vitamins A	B	C	D	P.P.	Calories
Corn meal	92	8.3	2.0	69.0	0.011	0.1225	0.0006	....	+	....	....	±	
Cane syrup	105	...	...	89.2	.....	.....	.....	...	+	..	...	+	
Flour	111	12.5	1.2	83.4	0.022	0.1030	0.0010	...	+	...	....	—	
Lard	81	...	81.0	...	.....	.....	.....	....	—	....	....	—	
Rice	25	2.0	0.1	19.6	0.0023	0.0240	0.0002	....	—	....	...	—	
Field peas	90	19.2	1.4	54.6	0.0756	0.0760	0.0052	+	++	....	....	+	
Hominy grits	51	4.3	0.3	0.3	0.0056	0.0734	0.0005	...	+	..	...	—	
Fat salt pork	60	1.1	51.3	51.3	0.0011	0.0115	0.0001	....	—	....	...	—	2890.0
Cheese	60	17.4	21.6	...	0.5586	0.4098	0.0007	++	++	....	....	+	264.0
Total		64.8	158.9	356.40	0.6762	0.8202	0.0083						3154.0

whom other deficiencies, especially B_1, co-exist. In these cases the appetite may not return until the patient is given B_1.[35] Occasionally the anorexia disappears while the patient is receiving nicotinic acid only to reappear some days later. The administration of B_1 at this point usually results in rapid improvement.[23]

Nausea and vomiting usually cease promptly after the administration of nicotinic acid. Diarrhea subsides more slowly, requiring 5 to 10 days for complete recovery.

The first published report showing the beneficial effect of nicotinic acid in the treatment of the psychoses of pellagra was by Smith, Ruffin and Smith in December, 1937.[28] Similar results have been obtained by other observers,[15,18,36] notably Matthews[18] and Spies and his associates.[36]

Patients with acute psychoses of short duration usually respond dramatically to nicotinic acid therapy. Even patients who have been completely disoriented and irrational may become entirely normal in as short a period as 4 to 5 days. The results are decidedly better than those obtained with liver therapy.

Nicotinic acid cures the cardinal symptoms of pellagra, but has only an indirect effect, by stimulating the appetite, on the associated secondary deficiencies.[17] Evidences of B_1 deficiency may appear while the patient is taking nicotinic acid as shown by our observations[23] and those of Spies.[35] The pellagrous seborrhea over the face and the perlèche-like lesions in the corners of the mouth respond less rapidly to nicotinic acid than to the whole liver extract, suggesting that they are caused primarily by other associated deficiencies in the B_2 complex. Sebrell and Butler's recent report indicates that the perlèche lesions are caused by a riboflavin deficiency, since they failed to respond to nicotinic acid and were subsequently cured by synthetic riboflavin.[25] The significance and etiology of the associated deficiencies in pellagra are being investigated at the present time.

The studies reported here indicate that nicotinic acid in small doses daily (1.5 mgm. per kilogram) is very effective in the cure of pellagra even when the patient is eating a deficient diet. For the routine treatment of pellagra as a disease we recommend the use of an adequate diet supplemented with other supportive measures as outlined in the next paragraph.

Severely ill patients, especially those with diarrhea and dementia, should be hospitalized invariably and treated as emergency cases. It is a common observation that patients of this type, even though they do not appear critically ill, may go into collapse and die within 24 hours. Probably the most important treatment in these cases is the prompt administration of glucose and saline intravenously. Continuous saline infusions may also be necessary to combat the dehydration. The diet in this stage of the disease is of little importance, as the acute glossitis, anorexia, nausea, and vomiting may prevent the ingestion of food or even of liquids. Yeast is obviously of little value. An aqueous liver extract (Valentine's liver extract), 30 cc. (1 oz.) t.i.d., is effective if it can be retained. The best treatment for such cases is the intravenous administration of nicotinic acid in doses of approximately 100 mgm. per day. This is most conveniently given by adding the nicotinic acid solution to the glucose and saline. This is continued until the gastro-intestinal symptoms have subsided, and then the patient is given a full liquid diet. After a few days a well-balanced diet is given. When the patient is able to eat, the intravenous treatment may be discontinued and the nicotinic acid given by mouth, 100 mgm. once or twice daily.

In our experience it is not necessary to treat the local lesions of pellagra. Mouth washes, wet dressings for the dermatitis, tincture of opium, and bismuth for the diarrhea are not only useless but may be actually harmful.

In a series of 251 patients treated in Duke Hospital, there have been 18 deaths, or 7 per cent mortality. This includes 7 patients who died either of pneumonia or generalized peritonitis. Since the introduction of nicotinic acid, 4 patients out of 108 have died, a mortality of 3.7 per cent. One of these was moribund on admission; another died of a generalized peritonitis.

BIBLIOGRAPHY.

1. BEAN, W. B.: Discussion of paper by Ruffin and Smith. South. Med. J., 32:47, 1939.
2. BLACKFORD, S. D.: The Treatment of Pellagra — A Critical Review. Va. Med. Monthly, 61:140, 1934.
3. BOGGS, T. R., AND PADGET, P.: Pellagra: Analysis of 102 Cases. Bull. Johns Hopkins Hosp., 50:21 (Jan.) 1932.

4. DANN, W. J., AND SUBBAROW, Y.: Differentiation of the Rat Dermatitis Factor and the Chick Dermatitis Factor from Nicotinic Acid. J. Nutrition, 16:183, 1938.
5. ELVEHJEM, C. A., MADDEN, R. J., STRONG, F. M., AND WOOLLEY, D. W.: Relation of Nicotinic Acid and Nicotinic Amide to Canine Blacktongue. J. Amer. Chem. Soc., 59:1767, 1937.
6. ELVEHJEM, C. A., MADDEN, R. J., STRONG, F. M., AND WOOLLEY, D. W.: The Isolation and Identification of the Anti-Blacktongue Factor. J. Biol. Chem., 123:137, 1938.
7. FOUTS, P. J., HELMER, O. M., LEPKOVSKY, S., AND JUKES, T. H.: Treatment of Human Pellagra with Nicotinic Acid. Proc. Soc. Exp. Biol. & Med., 37:405, 1937.
8. FOUTS, P. J., LEPKOVSKY, S., HELMER, O. M., AND JUKES, T. H.: Successful Treatment of Human Pellagra with the "Filtrate-Factor." Proc. Soc. Exp. Biol. & Med., 35:245 (Nov.) 1936.
9. FOUTS, P. J., AND ZERFAS, L. G.: Pellagra in Indiana and Its Treatment with Liver Extracts. J. Ind. Med. Assoc., 27:196, 1934.
10. FRANCES, R., BATES, R. D., BARKER, W. H., AND MATTHEWS, E.: Two Cases of Pellagra Treated with Nicotinic Acid. Bull. Johns Hopkins Hosp., 53:46, 1938.
11. GOLDBERGER, J., AND SEBRELL, W. H.: The Blacktongue Preventive Value of Minot's Liver Extract. Public Health Report, 45:3064, 1930.
12. GOLDBERGER, J., AND WHEELER, G. A.: Experimental Pellagra in the Human Subject Brought about by a Restricted Diet. Public Health Report, 30: 3336, 1915.
13. HADEN, R. L.: Multiple Specific Nutritional Deficiency Disease in the Adult. J. A. M. A., 106:261, 1936.
14. HARRIS, L., AND HASSAN, A.: Nicotinic Acid and the Pellagra-Preventing ("P.P.") Vitamin. Lancet, 2:1467, 1937.
15. HAWKSLEY, J. C.: A Case of Pellagra Treated with Nicotinic Acid. Lancet, 1:944, 1938.
16. MARGOLIS, G., MARGOLIS, L. H., AND SMITH, S. G.: The Cure of Experimental Canine Blacktongue with Optimal and Minimal Doses of Nicotinic Acid. J. Nutrition, 16:541 (Dec. 10), 1938.
17. MARGOLIS, L. H., MARGOLIS, G., AND SMITH, S. G.: Secondary Deficiency of Vitamin B_1 and Riboflavin in the Blacktongue Producing Diet. J. Nutrition, 17:63,1939.
18. MATTHEWS, R. S.: Pellagra and Nicotinic Acid. J. A. M. A., 111:1148, 1938.
19. RACHMILEWITZ, M., AND GLUECK, H. I.: Treatment of Pellagra with Nicotinic Acid. Brit. M. J., 2:346, 1938.
20. RAMSDELL, R. L., AND MAGNESS, W. H.: Parenteral Liver Extract Therapy in Pellagra. Amer. J. Med. Sci., 185:568, 1933.
21. RUFFIN, J. M., AND SMITH, D. T.: The Treatment of Pellagra with Certain Preparations of Liver. Amer. J. Med. Sci., 187:512, 1934.

22. RUFFIN, J. M., AND SMITH, D. T.: A Clinical Evaluation of the Potency of Various Extracts of Liver in the Treatment of Pellagra. South. Med. J., 30:4, 1937.
23. RUFFIN, J. M., AND SMITH, D. T.: Treatment of Pellagra with Special Reference to the Use of Nicotinic Acid. South. Med. J., 32:40, 1939.
24. SCHMIDT, H. L., AND SYDENSTRICKER, V. P.: Nicotinic Acid in the Prevention of Pellagra. J. A. M. A., 110:2065, 1938.
25. SEBRELL, W. H., AND BUTLER, R. E.: Riboflavin Deficiency in Men. Public Health Report, 53:2282, 1938.
26. SMITH, D. T.: Pellagra: Etiology; Response to a Deficient Diet. South. Med. and Surg., 94:134, 1932.
27. SMITH, D. T., AND RUFFIN, J. M.: Effect of Sunlight on the Clinical Manifestations of Pellagra. Arch. Int. Med., 59:631, 1937.
28. SMITH, D. T., RUFFIN, J. M., AND SMITH, S. G.: Pellagra Successfully Treated with Nicotinic Acid. J. A. M. A., 109: 2054, 1937.
29. SMITH, J. H.: The Treatment of Pellagra. South. Med. J., 27:163, 1934.
30. SMITH, S. G., MARGOLIS, G., AND MARGOLIS, L. H.: Effect of Autoclaving on the Vitamin Potency of Nicotinic Acid. Proc. Soc. Exp. Biol. & Med., 38:251, 1938.
31. SPIES, T. D.: Pellagra: Improvement While Taking the So-called "Pellagra Producing" Diet. Amer. J. Med. Sci., 184:837, 1932.
32. SPIES, T. D.: Pellagra: An Experimental Study of the Skin Lesions. Proc. Soc. Exp. Biol. & Med., 30:1227, 1933.
33. SPIES, T. D.: The Treatment of Pellagra by Means of Parenteral Liver Extract. Proc. Soc. Exp. Biol. & Med., 31:363, 1933.
34. SPIES, T. D.: The Treatment of Pellagra. J. A. M. A., 104:1377, 1935.
35. SPIES, T. D., AND ARING, C. D.: The Effect of Vitamin B_1 on the Peripheral Neuritis of Pellagra. J. A. M. A., 110:1081, 1938.
36. SPIES, T. D., ARING, C. D., GELPERIN, J., AND BEAN, W. B.: Mental Symptoms of Pellagra: Their Relief with Nicotinic Acid. Amer. J. Med. Sci., 196:461, 1938.
37. SPIES, T. D., BEAN, W. B., AND STONE, R. E.: The Treatment of Subclinical and Classic Pellagra: Use of Nicotinic Acid, Nicotinic Acid Amide and Sodium Nicotinate with Special Reference to the Vasodilator Action and the Effect on Mental Symptoms. J. A. M. A., 111:584, 1938.
38. SPIES, T. D., CHINN, A. B., AND MCLESTER, J. B.: Severe Endemic Pellagra. J. A. M. A., 108:853, 1937.
39. SPIES, T. D., COOPER, C., AND BLANKENHORN, M. A.: Nicotinic Acid in the Treatment of Pellagra. J. A. M. A., 110:622, 1938.
40. SYDENSTRICKER, V. P., SCHMIDT, H. L., FULTON, M. C., NEW, J. S., AND GEESLIN, L. E.: Treatment of Pellagra with Nicotinic Acid; Observations in Forty-five Cases. Sou. Med. J., 31:1155, 1938.
41. VOEGTLIN, C.: Recent Work on Pellagra. Public Health Report, 35:1435, 1920.
42. WYLIE, W. D.: The Treatment of Pellagra. Sou. Med. & Surg., 97:14 (Jan.) 1935.

DISCUSSION.

DR. THOMAS T. MACKIE (New York, N. Y.): Mr. President, I imagine very few men who are working in the North have any appreciation of the magnitude of this problem of pellagra, not only in our Southern States, but in a good many other parts of the world. Despite the modesty with which Dr. Smith referred to the matter of priority and specifically the similarity of the dates of publication of the original reports, I feel very strongly, having followed all this work very closely myself, that Dr. Smith and Dr. Ruffin are not given anything like the credit which is due them for a perfectly magnificent piece of work. Perhaps it would be better to say, as he intimated this morning, their observations on the mechanism and treatment of pellagra have been controlled, I think, far better than most other studies that have been made and published of this condition.

I would like to comment, if I may, very briefly, upon the type of pellagra which we see in the North. I am inclined to think that one may say, roughly speaking, there are three general types: the endemic form, as Dr. Smith and Dr. Ruffin see it in the South; the alcoholic pellagra, as one sees it in the North; and then the pellagra which I have seen most of, occurring as one of the manifestations of mixed deficiency disease of other types. Certainly this latter group is not comparable to the alcoholics. Certainly it is not comparable, either, in its total clinical picture nor in the actual severity of the pellagra itself, to the form which is encountered in the South. I am not at all sure, however, that the endemic southern form of pellagra is quite as pure an entity etiologically as Dr. Smith intimated this morning. For example, the lesions which occur at the corner of the mouth have been, I think, pretty definitely shown to be a riboflavin deficiency and to clear up within certainly five to seven days time on very small dosage of crystalline riboflavin.

I would like to ask Dr. Smith whether in these cases with the mouth lesions they have tried riboflavin therapeutically in addition to their nicotinic acid, and whether they have made any urinary studies.

DR. HARRY A. BRAY (Ray Brook, N. Y.): I would like to ask Dr. Smith what are the factors of sunlight which produce exacerbation of the disease.

DR. ERNEST B. BRADLEY (Lexington, Ky.): Mr. Chairman, I didn't understand exactly about the coramine. I couldn't hear very well. One patient, he said, was given coramine. I didn't understand whether that was instead of or supplementary to the treatment with nicotinic acid.

DR. CHESTER M. JONES (Boston, Mass.): I would like to ask Dr. Smith a question. I saw some of these patients with him last spring and at the time I had the impression that these lesions around the nose might also be associated with riboflavin deficiency. I wonder if he would say anything about that.

DR. DAVID T. SMITH (Durham, N. C.): Mr. President, Dr. Mackie has been very kind in his discussion of the paper and I am glad he brought up the question of the riboflavin. We have been making observations for several years on the things I pointed out as what we consider accessory lesions of pellagra, because they are not constant. Those cracks in the corners of the mouth and the sebaceous glands may show definite improvement in three or four days with

yeast or liver, crude liver, and it is true that Dr. Sebrell has published data on the production of cracks in the corners of the mouth under experimental conditions in human beings and their healing in seven days to two weeks. I asked him the question how he could with justification attribute to the pure crystalline substance the sole etiology when it took longer for the pure material to do it than when we were formerly curing them with crude material. His answer was that he hadn't given enough, he had only given 5 or 7 milligrams. We have been giving 50 milligrams and they heal; but I am still worried about it for the reason that the patient who developed this under our eyes, eating a deficient diet, healed with no treatment but nicotinic acid. It took him twice as long as it would have with yeast or liver, suggesting that it was the increased appetite, the increased utilization of materials already in the basal diet which he wasn't getting because he wasn't eating enough.

Recently we have had a chance to try one patient with pure B_6, synthetic B_6, with cracks in the corners of the mouth, and that patient made a 50 per cent improvement in twenty-four hours, and we have it recorded on the film. I wouldn't believe it otherwise. But I suspect that there is a riboflavin element in it. There may also be a B_6 element necessary and there may also be a nicotinic acid element necessary, because nicotinic acid has been given before the riboflavin was given to show that it wasn't a nicotinic acid deficiency, but it ought to be also done the other way around, because we may have a combination effect.

Dr. Bray asked how the sunlight lights up these pellagrins. I don't know. We can make a good case by analogy by photosensitivity; the fact that porphyrins in the body, increased porphyrins, make a patient susceptible to sunlight is supported in the case of pellagra by some studies at Duke and some by Rhodes at the Rockefeller Institute, who has demonstrated increased porphyrin secretion or excretion in the urine and stool. So that it is very tempting to say the problem is very simple, that the pellagrin doesn't oxidize out his normal porphyrins the way a normal individual does and they accumulate in his skin, and then he gets out in the sunlight and the sun lights him up. Then you treat him with liver or nicotinic acid and restore his oxidative mechanisms to normal, and then he no longer has any porphyrin to light him up. But that is very much on the speculative side and not proven.

Dr. Bradley asked about coramine. Coramine was the sole treatment of these patients. It was used as a substitute for nicotinic acid because the chemical formula of coramine shows that it is nothing more than nicotinic acid amide with two extra ethyl groups hitched on to it. We have assayed the coramine carefully in dogs, the same as we did with the nicotinic acid, and found that 10 per cent of the coramine is as effective as nicotinic acid. It has many clinical advantages over nicotinic acid. It doesn't produce the violent blushing reaction the patients get with nicotinic acid. It is much more soluble, so 3 cc. of the material intramuscularly is enough per day. It is available in northern hospitals and around over the country already, sterile and ready for injection in the way nicotinic acid is not commonly available.

Dr. Jones mentioned the nose lesion which I partly covered in answering Dr. Mackie. We are still working on it with the newer material, like pure riboflavin and pure B_6. We hope to be able to find out which one or which combination is the cause of it.